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AND THE SCIENCES
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Warburg Apparatus Used in Tissue
Metabolism Test in
LaWall Memorial Laboratory (See Page 269)

Since 1825 August 1952

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CONTENTS

E D I T O R I A L

SUBSTITUTION—A THREAT TO OUR PROFESSION

WE were amazed and a little stunned when we heard at a recent meeting a report on the extent to which substitution is practiced in retail pharmacies. While we knew that some few unscrupulous operators were guilty of this fraud, their number was believed to be no larger than that of the shysters in other professional areas. In this belief we were totally wrong and it was with no little bitterness and chagrin that we were forced to accept the existence of this pharmaceutical malpractice to an extent that makes us ashamed to be identified with those who hold their professional integrity so lightly. We shall not give the actual figures, in terms of the percent of pharmacists who were found guilty of substitution by this survey, since such data would provide strong evidence against us by those forces which already are seeking to undermine our professional status. It is indeed ironic that our profession, like some others, is losing its standing and recognition from forces within the profession rather than from without. The situation is quite analogous to that in which we as Americans are losing our liberty so hard won in the past.

The motive behind substitution is always the same—more profit. Some pharmacists will attempt to justify the substitution of an inferior make of some drug when a well-known brand is prescribed by explaining that the product prescribed is over-priced and that they were just trying to save the customer money and reduce the cost of medical care. This sounds well, but when the charge made to the patient is investigated it is almost invariably found that the charge was based on the cost of the well-known brand and not the substitute actually dispensed.

We have in manufacturing pharmacy, today, some questionable companies which were formed, and which operate, only to exploit the avarice and greed of certain retailers. They offer merchandise, often closely resembling a branded product, at a lower cost and encourage the retailer to substitute their products on prescription. We have seen a number of such products and we know something

of the operators who prepare them. In their moral outlook they have sneak thieves, narcotic peddlers and procurers as companions.

While it may seem that certain specialties and proprietary products are costly and over-priced it must be remembered that pharmaceutical research, development and large scale distribution is also expensive. Often, a company will spend hundreds of thousands of dollars in developing some new drug. This is followed by months of costly clinical trial and then, if efficient and safe, extensive detailing to acquaint the medical profession with its properties and uses. It is absolutely essential that this heavy investment be recovered through sales of the product. Furthermore, not all research is successful and the failures must also be amortized by the sale of the successes.

If fly-by-night companies, aided and abetted by unethical pharmacists, deprive the ethical manufacturer of his proper return by supplying a cheap substitute, the whole mechanism of progress through research is wrecked with everyone the loser. Even the courts have recognized that such an act of substitution damages the property rights of the manufacturer and he can, if he wishes, seek redress by court action.

The better manufacturers have endured the substitution damage inflicted upon them with great restraint for they dislike taking legal action against pharmacists with whom they try desperately to maintain good relations. The amount of substitution, however, has grown to such proportions that some steps to correct the situation cannot long be postponed.

The legal implications of substitution are not the most serious if one studies this situation carefully. It is difficult to think of something that could more seriously harm our professional prestige than to have it known, generally, that substitution is a common practice. Nothing would cause physicians to dispense their own medicines or to operate a clinic pharmacy more quickly than to lose faith in the integrity of the pharmacist. Nothing would create worse public relations for pharmacy than the continuation and exposure of this pernicious practice. Finally, nothing could more certainly bring about a further invasion of our professional prerogatives by government. We now have so few left, surely we should cherish what remains.

Time and again we have recorded pharmacy's failure to measure up to the full stature of professionalism. Cannot the tide be turned?

Is our profession to wither and die? Pharmacists must face this problem squarely and honestly with a full understanding of its moral and legal aspects. There must be a more adamant stand taken by our professional organizations to police themselves and expel those who betray the profession. Otherwise we shall need no such organizations. Pharmacy will operate following a book of rules laid down by government, and with inspectors everywhere to see that they are obeyed. Possibly those who extol the virtues of the Durham-Humphrey Amendment would find such additional regimentation stimulating. On the other hand those who love the profession would find in such legislation their total defeat and disillusionment.

L. F. Tice

USES AND FORMULATIONS OF SOME SYNTHETIC ORGANIC INSECTICIDES

By A. A. Dodge *

A FACTOR of prime importance to anyone contemplating the manufacture and distribution of insecticides is the compliance with the legal requirements involved. These are summarized by De Ong in his book on insecticides, the title of which is listed in the attached bibliography of references.

In 1947 the "Federal Insecticide, Fungicide, and Rodenticide Act" was passed, superseding the Federal legislation previously in force. Among the provisions of this Act is the legal definition of the term "Economic Poison" as any substance used against insects, fungi, weeds, and other pests. "Rodenticide" refers to substances used against rodents or other vertebrate animals listed as pests. "Labeling" refers not only to the attached label but also to literature referring to the label which may accompany the economic poison.

Provision is made for the addition of a distinctive color to such potent substances as the arsenicals and certain fluorine compounds. The registration of economic poisons in interstate commerce is also required. The Act also includes restrictions on the sale of broken or unsealed containers, as found in a number of state laws.

In addition to the provisions of the Federal Act mentioned, insecticides are subject to the following Federal regulations: (1) Interstate Commerce Commission Regulations for Transportation of Explosives and Other Dangerous Articles; (2) Federal Caustic Poison Act and Regulations: Food and Drug Administration, Federal Security Agency; (3) Agricultural Marketing Administration, U. S. Department of Agriculture; (4) Federal Food, Drug and Cosmetic Act and Regulations: Food and Drug Administration, Federal Security Agency; and (5) U. S. Post Office Regulations.

Classification of Insecticides. Insecticides are most frequently classified according to the manner in which they kill insects, *i.e.*, (1) stomach poisons, (2) contact insecticides, and (3) fumigants. To some extent there may be an overlapping, since certain substances

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may kill in two or even in all three ways. Stomach poisons are used for the control of insects which possess biting or chewing mouth parts. By applying the insecticide in the form of a dust or spray to the plant surface upon which the insect feeds, it follows that the poison will be ingested into the alimentary tract. To be effective, such an insecticide should be insoluble in water and ought to be capable of withstanding chemical decomposition for a considerable period of time when exposed to the sunlight and air. Stomach poisons are chiefly inorganic in nature; common examples are the arsenates of lead and calcium, Paris green, cryolite (a fluorine compound), sodium fluoride, and such arsenicals as arsenic trioxide and sodium arsenite, the latter two being used in poisoned baits to destroy ants, grasshoppers, etc.

In order to kill insects which are not surface-feeders, *e.g.*, the aphids, it is necessary to apply the insecticide directly to the insect or else to the surface upon which the insect moves (residual treatment). These are the contact insecticides, and such synthetic compounds as DDT, chlordane, aldrin, dieldrin, methoxychlor, the organic phosphates and numerous others are included in this category. Whether applied as dusts or sprays, these substances possess the great advantage of residual action, leaving a film of insecticide upon the surface which will be either toxic or lethal to any susceptible insect coming into contact with it within a period of time which may extend into several weeks, depending upon various conditions. The contact insecticides vary considerably in their volatility, and some of them may kill by a fumigant action after entering the respiratory system of the insects.

Fumigants are useful in closed spaces such as chests, bags, or closets for clothing in the home, for which purpose naphthalene flakes or balls ("moth balls") and paradichlorobenzene ("Dichloricide" Merck, and other brands) have long been used. For special purposes, such as in warehouses, mills, green-houses, the holds of ships, etc., toxic gases may be released to provide the desired concentration (*e.g.*, hydrocyanic acid gas) or volatile substances such as carbon disulfide, methyl bromide, ethylene dichloride or dibromide, propylene dichloride, and orthodichlorobenzene may be used. Some of the latter compounds are excellent soil fumigants.

It would be impossible to consider here all of the substances which are used as insecticides, and therefore this discussion will be

limited to several of the synthetic organic compounds most commonly employed for that purpose.

DDT. The substance now known popularly as DDT was first synthesized and described by Zeidler in 1874, but its possibilities as an insecticide remained unknown until 1939, at which time a group of Swiss investigators searching for new compounds to use for that purpose repeated Zeidler's work. The results of their tests were so striking that they patented their discovery in Switzerland in 1940. An English patent was also granted to them, and in 1943 a U. S. patent was issued, covering the use of diluents or carriers. DDT proved to be quite unique in its relative stability, long residual action, cheapness and ease of manufacture, and effectiveness against a great variety of insects. Doubtless the extensive use of this substance by the Armed Forces during World War II gave impetus to its later use by the public; and despite the fact that numerous other insecticides have appeared on the market since then, the general popularity of DDT has not been seriously affected.

The term "DDT" is an abbreviation of the chemical name dichlorodiphenyl-trichloroethane; the compound is more precisely named 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane. The technical grade of the chemical consists of a mixture containing usually from 70 to 77% of the desired compound (designated as *p,p'*-DDT), together with variable amounts of two isomers (*o,p'*-DDT and *o,o'*-DDT) and traces of numerous other compounds. It has been found that the *p,p'*-isomer possesses more insecticidal potency than the other isomers. For most purposes the technical grade is satisfactory, although for use in aerosol bombs a more highly refined grade containing a higher percentage of the *p,p'*-isomer is preferred.

Technical DDT occurs as a white, amorphous powder which is almost completely insoluble in water. It is quite soluble in numerous organic solvents; small amounts of xylene, methylnaphthalene, cyclohexanone, or other suitable liquids are frequently used to enhance the limited solubility (about 4%) of DDT in deodorized kerosene in the formulation of household space sprays or aerosol bombs.

Since DDT does not possess a quick knockdown (*i.e.*, the ability to stun or incapacitate insects within a short time after application), it is necessary to impart this property by incorporating some other substance such as a pyrethrum concentrate, an aliphatic thiocyanate (*e.g.*, the "Lethane" series of insecticides marketed by Rohm and

Haas), or "Thanite" (produced by the Hercules Powder Company, and consisting of the thiocyanoacetates of bornyl and fenchyl alcohols).

A formulation for a satisfactory household space spray recommended by the Pittsburgh Agricultural Chemical Company consists of the following (percentages given by volume):

20-1 Pyrethrum extract or equivalent	5.00%
30% DDT oil concentrate	1.25%
Petroleum hydrocarbon base oil	93.75%

The "20-1 pyrethrum extract" referred to consists of a solution of the oleoresinous extractive of pyrethrum in a suitable organic solvent and containing a specified percentage of pyrethrins, the active constituents of this drug. One of the commercially available preparations of this type is "Pyrefume Super 20" Penick, which contains 2.5% of pyrethrins dissolved in deodorized kerosene.

The 30% DDT oil concentrate specified in the formulation affords a convenient method for incorporating the insecticide in oil-base sprays. As offered for sale by the Pittsburgh Agricultural Chemical Company, it contains 30% by weight of technical DDT dissolved in aromatic petroleum derivatives.

Other commercially available DDT formulations include emulsifiable concentrates of 25% and 30% strengths, dust preparations of 5%, 10%, and 50% strengths, and wettable powders of 50% and 75% strengths intended for the preparation of sprays or dips.

For the preparation of a dip or spray for beef cattle or dairy cattle which are not being milked, it is recommended that 4 pounds of the 50% wettable DDT powder be thoroughly mixed with from 50 to 100 gallons of water. An oil solution of DDT should not be used on livestock since the skin absorbs it.

For garden, field, and orchard use, the amount of the 50% wettable powder necessary to control nearly all susceptible insects may be reduced to 2 pounds per 100 gallons of water.

The recommended percentage of DDT formulated as a dry dust for the control of fleas and ants is 10%; for lice on animals (except cats) 5% is considered sufficient.

When formulating DDT in a dust, wettable powder, or spray, the user must make a judicious choice of diluent or solvent, as it has been shown that it is incompatible with alkalies, undergoing a

chemical change and losing much of its potency. Contact with iron or aluminum containers must be avoided for the same reason. If DDT sprays are applied to freshly whitewashed surfaces, the insecticide will not give effective residual control.

DDT is incompatible with kaolin, fuller's earth, and nicotine; slight decomposition is caused by bentonite, some talcs and pyrophyllites, sulfur, Bordeaux mixture, and the fungicide "Fermate" Du Pont. It is considered to be compatible with kieselguhr, chalk, gypsum, the arsenates of lead and calcium, Paris green, cryolite, the fluosilicates, and pyrethrum.

It is strongly recommended that DDT preparations should not be used in barns where cattle are milked, lest the insecticide either contaminate the milk or be ingested by the animals. Feeding experiments conducted on dairy cows have demonstrated that DDT tends to accumulate in the fatty tissues of animals and also appears in the butter fat of the milk. If grazing crops have been treated with DDT, milking cows and beef cattle which are soon to be slaughtered should be kept out of such areas for at least two weeks after the insecticide has been applied.

It would not be feasible to list the many insect pests against which DDT has been found effective; however, it may be of interest to enumerate several which this insecticide fails to control: apply sawfly, black aphid, California red scale, cotton boll weevil, cotton leafworm, Mexican bean beetle, orchard mite, red spider, snails, and the woolly aphis.

Chlordane. "Chlordane" is the name applied by the U. S. Department of Agriculture to a chlorinated hydrocarbon having the descriptive chemical title 1,2,4,5,6,7,8,8-octachloro-4,7-methano-3a4,7,7a-tetrahydroindane. The technical grade of chlordane commercially available consists of a mixture containing from 60% to 75% of the chemical just named, together with from 25% to 40% of several other related compounds.

The empirical formula of the chief constituent of technical chlordane is $C_{10}H_6Cl_8$, a fact which let the Velsicol Corporation, producer of this insecticide, to secure the trade-marked designation "Velsicol 1068." Technical chlordane is a dark colored, viscous liquid with a sp. gr. of 1.59-1.63 at 25° C. It is insoluble in water, but is soluble in all proportions in organic solvents.

Chlordane is capable of acting in three ways: as a contact insecticide, as a stomach poison, and under some conditions as a fumigant. For the formulation of a chlordane spray for household use, deodorized kerosene is commonly used as the solvent, the concentration of insecticide being about 2%. Such a spray is useful for the control of roaches, ants, crickets, ticks, fleas, silverfish, the so-called "waterbugs," etc. Chlordane not only produces a high initial kill of these insects, but also according to some investigators has a residual effect lasting for several months. This insecticide is, however, not rapid in its initial action, and it is therefore desirable to incorporate another material capable of providing quick knockdown. The same products that were mentioned in connection with DDT household spray formulations are also satisfactory for use with chlordane.

A well-known proprietary preparation of this type is "Cook-Kill Bug Killer"; this contains the "Velsicol 1068" brand of chlordane and pyrethrins in a light oil base, presumably of the kerosene type.

Chlordane formulations are also extensively used for the control of many insect pests attacking garden, field, or orchard crops and for eradicating numerous livestock parasites. Various firms market chlordane dusts in either a 5% or 10% concentration, a 40% wettable powder, a 20% oil concentrate, and a 40% emulsion concentrate. The dusts consist of a free-flowing powder in which the chlordane has been taken up by a clay or talc and is ready for application in that form. The 40% wettable powder contains 40% by weight of technical chlordane plus 3% to 5% of a suitable wetting agent. For use, it is mixed with sufficient water to yield a suspension which can be readily sprayed on vegetation or on livestock. The concentration usually recommended is 5 pounds of a 40% wettable powder per 100 gallons of water, which would represent an actual chlordane content of 2 pounds per 100 gallons of water.

The 40% emulsion concentrate is prepared by mixing the required amounts of chlordane and kerosene and adding 10% of a wetting agent. To retard creaming, starch or dextrin is added. Such concentrates are intended to be diluted with water to yield an emulsion containing 2% of chlordane; to obtain this concentration, 1 quart of a 40% emulsion concentrate should be added to 100 gallons of water.

For field crops, either the dust or aqueous emulsion formulations can be used. Chlordane is effective against grasshoppers, cutworms, and numerous other field crop insects. For use on livestock,

the wettable powder or aqueous emulsion formulations are recommended; such treatment will control mange mites, ticks, lice, and certain other insects. Authorities caution, however, that chlordane should not be used in dipping vats, and that care must be exercised in applying it to young animals under four months of age. For the control of lice on beef cattle or other cattle not being milked, a concentration of 2½ pounds of a 40% wettable powder per 50 gallons of water is recommended, and is to be used as a spray or wash. For dairy cattle a formulation of lindane, methoxychlor, or rotenone is advised in preference to chlordane.

It has been well established that chlordane must not be formulated with alkaline materials, including alkaline wetting agents, since it undergoes dehydrohalogenation (a splitting off of hydrogen chloride) under such conditions, with consequent loss of insecticidal potency. Any emulsifier or wetting agent selected, therefore, should be non-alkaline, non-ionic, and oil-soluble. Chlordane is known to be incompatible with lime and lime-sulfur, and probably also with Bordeaux mixture and soap. Its compatibility with nicotine and calcium arsenate has been questioned. In addition, chlordane or its liquid preparations should not be stored in galvanized iron or steel containers, but rather in glass, aluminum-clad, or lacquered steel containers.

In November, 1951, it was announced that the Production and Marketing Administration of the U. S. Department of Agriculture was revising its instructions to manufacturers of household type insecticides containing chlordane. The revised instructions will limit label recommendations to roaches, ants, and a few other pests. No label directions will be permitted for the general treatment of large areas, for the household use of mist sprays, nor for the treatment of furniture or clothing.

The use of chlordane on food crops is not recommended, and any extensive use in dwellings has been limited by the volatile nature of the compound.

Aldrin. Aldrin, formerly called Compound 118, is manufactured by the firm of Julius Hyman and Company, Denver, and by arrangement with the manufacturer is distributed by the Shell Chemical Corporation and other outlets. It contains not less than 95% of the compound 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethano-naphthalene; its empirical formula is $C_{12}H_8Cl_6$.

It is a white, crystalline material, insoluble in water, but readily soluble in deodorized kerosene and in most other organic solvents.

Aldrin possesses the unique advantage over many other halogenated hydrocarbon insecticides of being stable in the presence of strong alkali or metallic chlorides. It is also considered stable in sunlight and air. Compared with chlordane in equally effective doses, aldrin appears to be slightly slower in action and to have approximately the same degree of residual activity.

Aldrin is commercially available in both dust and emulsifiable concentrate form. Formulations on the market for cotton dusting include various combinations, *e.g.*, (1) aldrin 2½% and DDT 5%, (2) aldrin 2½%, DDT 5%, and sulfur 40%, and (3) aldrin 2½% and sulfur 40%. Emulsifiable concentrates commercially available for the preparation of sprays contain the equivalent of 2 pounds of aldrin per gallon, or else of 1 pound of aldrin and 2 pounds of DDT per gallon.

The Hyman company has issued cautionary statements regarding the handling of aldrin by workers engaged in preparing its formulations. The required safety measures include daily laundering of work clothing, the wearing of rubber gloves and efficient respirators, provision for adequate ventilation, etc.

For the preparation of an aldrin emulsifiable concentrate containing (1) the equivalent of 2 pounds of aldrin per gallon, or (2) the equivalent of 1 pound of aldrin and 2 pounds of DDT per gallon, the manufacturer recommends the following formula, in which the aldrin is incorporated in the form of a 60% aldrin equivalent solution which he supplies:

(1) 60% Aldrin equivalent solution	3.33 pounds
Emulsifier	0.83 pound
Paraffinic or aromatic solvent	
To make	1.00 gallon
(2) 60% Aldrin equivalent solution	1.66 pounds
DDT	2.00 pounds
Emulsifier	0.83 pound
Aromatic solvent	
To make	1.00 gallon

Nonionic emulsifiers are recommended for use in the above formulations because the use of hard water with such concentrates does

not affect their emulsifiability, and also because such emulsifying agents do not react chemically with aldrin even upon prolonged storage. Among the proprietary nonionic agents recommended by the Hyman company are the following: "Antarox A-200", "Atlas 1256", "Atlox 1045-A", "Base 401-M", "Emulside-65", "Emcol H-77", "Glycox-1300", "Igepal 300", "Monsanto Emulsifier-L", "Nopco Agrimul-11", "Sharples-5037", "Skil 234-B", "Trem-615B", and "Triton X-100".

The solvents recommended are "Shell Aromatic" (sp. gr. 0.891), xylol (sp. gr. 0.867), Diesel oil (sp. gr. 0.828), deodorized kerosene (sp. gr. 0.800), and light petroleum oil (sp. gr. 0.744).

Since aldrin is considered to be highly poisonous, its use on food crops or on animals is not recommended. Recently the U. S. Department of Agriculture approved the use of aldrin against soil insects such as white grubs, rootworms, and wireworms. The Shell Chemical Corporation states that as little as 4 ounces of aldrin per acre on mature cotton will control the boll weevil and several other cotton pests, and that in the early season from 1 to 2 ounces per acre is sufficient.

The Hyman company states that for interstate shipment of aldrin, 60% aldrin equivalent solution, and formulations of these basic materials, each manufacturer is required by Federal legislation to register his products with the Insecticide Division, Livestock Branch, Production and Marketing Administration of the U. S. Department of Agriculture. In the brochure titled "Formulators' Manual" published by this company are included specimen labels complying with the legal requirements. For example, the label must carry the percentage composition of the product, poison statements (including internal and external antidotes and the necessary precautions in handling and use), inflammability warning (where an inflammable solvent is used), and the directions for use. It is advised that proposed labeling should be submitted to the U. S. Department of Agriculture prior to use on interstate shipments, and that state laws should also be checked.

Dieldrin. This chemical is a close chemical relative of aldrin, being the 6,7-epoxy derivative of the latter. As produced commercially by the Hyman company, it is an odorless, white, crystalline compound with a purity of at least 85%. Its empirical formula is $C_{12}H_8Cl_6O$, and it has the descriptive name 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4,5,8-dimethanonaphthalene.

Dieldrin is insoluble in water, but is moderately soluble in the usual organic solvents with the exception of methyl alcohol and the kerosene fractions of petroleum.

Although dieldrin is affected by strong acids, it is stable toward weak acids and toward alkalies. It can be used in combination with other insecticides and with fungicides. It acts as a contact insecticide, exhibiting a remarkable residual toxicity. Compared with lindane, its action is slower, but far more persistent; in this respect, it surpasses even DDT. Dieldrin is considered to be highly poisonous, and great care in its handling is urged. Its use on food crops or on animals is to be avoided.

It has been suggested that its residual toxicity may be valuable in controlling flies and mosquitoes, fabric pests, cotton insects, forestry pests, termites, pests in the soil, pests in lumber products, and industrial pests not infesting food products.

BHC and Lindane. Benzene hexachloride, abbreviated as BHC, has the empirical formula $C_6H_6Cl_6$, a fact which led to the synonym "*666*". Although synthesized by the chlorination of benzene, the reaction products do not contain the benzene nucleus; the substance is more precisely, but perhaps less conveniently, named 1,2,3,4,5,6-hexachlorocyclohexane. Another designation for it, "Gammexane", has been registered as a trade-mark.

The technical grade of BHC is a white powder with a persistent, musty odor and consists of a mixture of at least five isomers designated as alpha, beta, gamma, delta, and epsilon, together with small amounts of other compounds. The gamma isomer has been demonstrated to be the chief insecticidal component of the mixture; in the technical grade of BHC it is present to the extent of 11% to 15%. Through the use of appropriate organic solvents, the gamma isomer may be isolated from the mixture; the designation "lindane" is now used for a product containing not less than 99% of this isomer.

Both technical BHC and lindane possess all three types of insecticidal activity: contact poison, stomach poison, and fumigant.

Commercially available lindane preparations include emulsion concentrates of 20% and of 11% to 12.9% strengths and wettable powders of 25% and 12.5% strengths, all of which are intended for dilution with water for application as sprays. A 1% dust for use on livestock is also marketed.

It is important to avoid alkaline substances in BHC and lindane formulations since dehydrohalogenation readily occurs, with consequent loss of insecticidal potency.

It has been noted that potatoes may acquire a musty taste if excessive amounts of BHC are applied to the soil or to the plants. Peas and some varieties of beans should be treated before the bloom appears. On apples, peaches, plums, and cherries BHC or lindane should not be used later than from four to six weeks before the ripening period.

For the control of cotton pests, the U. S. Department of Agriculture recommends a dust called "3-5-40" which contains 3% of the gamma isomer of BHC, 5% of DDT (for bollworm control), and 40% of sulfur (for red spider control). Five applications per season are advised, at rates varying from 8 to 15 pounds per acre.

Many types of chewing or sucking insects attacking field crops can be controlled by treatment with a dust containing 1% of gamma BHC, applied at a rate of 20 to 40 pounds per acre.

The aqueous sprays prepared from lindane emulsion concentrates or wettable powders are recommended for the control of flies, roaches, ants, and mosquitoes in and around the buildings on dairy farms. Specified strengths of such sprays are also used for controlling insect pests on livestock. It is now well established that lindane is capable of killing flies which have become resistant to DDT. Lindane has received the approval of the U. S. Department of Agriculture for use against flies in dairy barns and for direct application to dairy cattle for the control of mange.

Soon after technical BHC came into extensive use it was noted that if dilutions of this insecticide were dusted on poultry for the control of lice and mites, the flesh of the fowls and even the eggs acquired a musty taste. The limitation has since been overcome by treating the roosts with commercially available oil-based solutions, which kill the insects by fumigant action.

Toxaphene. This insecticide, a product of the Hercules Powder Company, is synthesized by chlorinating the terpene hydrocarbon camphene, which is prepared from turpentine oil. Toxaphene is a light amber colored, waxy solid with the approximate empirical formula $C_{10}H_{10}Cl_8$; it is insoluble in water but readily soluble in the usual organic solvents including refined kerosene. Since the

substance has one labile chlorine atom, combinations with alkaline materials should be avoided.

Toxaphene is relatively slow in its action, but it has the advantage of a prolonged residual effect. Commercially available formulations include 20% and 40% dusts, 20-40 dust mixture (containing toxaphene 20% and sulfur 40%), and liquid emulsifiable concentrates containing 4, 6, or 8 pounds of toxaphene per gallon which are used for preparing sprays.

For control of the boll weevil, bollworm, cotton aphid, cotton leafworm, and Southern stink bug, the general recommendation is the application of 10 pounds per acre of a 20% toxaphene dust, such treatment being repeated several times during the season. The use of the 10% dust at the rate of 10 pounds per acre per application is considered adequate for the cotton fleahopper, rapid plant bug, tarnished plant bug, and thrips. If red spider is present, 40% or more of dusting sulfur should be included in the toxaphene dust formulation.

For control of the armyworm, the U. S. Department of Agriculture recommends the use of the 20% toxaphene dust at the rate of 10 to 20 pounds per acre, or of a spray representing 2 pounds of actual toxaphene per acre. Such a spray is also effective for cutworms on corn. For controlling grasshoppers the U. S. D. A. recommends the application of 1 to 1½ pounds of actual toxaphene per acre when used as a spray, or from 1½ to 2½ pounds per acre when used as a dust. Such treatments have been shown to give high initial kills and to have a residual action lasting 1 to 3 weeks. A satisfactory poison bait may be prepared by mixing 1 pound of toxaphene with 100 pounds of coarse bran, distributing the bait at the rate of 5 to 10 pounds per acre.

The U. S. D. A. recommends toxaphene for the control of ticks, lice, and horn flies on all livestock except dairy cattle. The insecticide is applied as a 0.5% spray.

For a more complete list of recommended uses of toxaphene, literature available from the Hercules Powder Company should be consulted.

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Consult "Pesticide Handbook" for list of manufacturers and their products.

THE EFFECT OF SPOILED FRUIT ON TABLE TYPE LOGANBERRY, GRAPE AND APPLE WINES

By Edward Krupski, Nathan A. Hall and Louis Fischer *

ALTHOUGH the quality of the fruit is not always controlled as rigorously as is possible, the best wine is made from good and sound fruit. When the storage of fruit has been faulty, it becomes undesirable for table use and may be channelled into the production of wines in order to avoid loss.

Numerous studies upon the deterioration of fruits used in wine making have been made (1-23), and the condition of the fruit from which wine is made will continue to be a matter of concern. Almost all investigations of wine have been limited to grape wine. This study was undertaken to show the effect, if any, of the use of decomposed fruit in wine making and to ascertain whether or not certain constituents commonly determined in alcoholic beverages by accepted analytical and control procedures would be affected.

Experimental

Preparation of Samples

Each lot of fruit was divided into four portions, and wine was made from each portion at progressive stages of decomposition as the fruit was allowed to decompose at room temperature. According to practice in the State of Washington, each must was sulfited, ameliorated with dextrose syrup to attain alcoholic concentration by fermentation, fermented, sweetened with sucrose, filtered, bottled and pasteurized. Samples were removed as necessary for analysis, and the remainder of each opened bottle was discarded.

Procedures

All procedures used were those outlined in the Methods of Analysis of the Association of Official Agricultural Chemists (A. O. A. C.), 7th Edition, 1950, unless otherwise specified. Measurement of pH was made with a Beckman Model H pH meter. Glycerol was de-

* College of Pharmacy, University of Washington, Seattle, Washington.

TABLE I.

Analysis of Wines

Wine Type	Loganberry				Grape—Island Belle				Apple			
Condition of Fruit Used*	Good	Fair	Poor	Very Poor	Good	Fair	Poor	Very Poor	Good	Fair	Poor	Very Poor
pH	3.19	3.86	3.31	3.28	3.34	3.30	3.30	3.53	3.55	3.63	3.51	3.47
Ethanol per cent by volume	11.4	11.0	10.8	13.2	12.1	13.3	13.0	11.9	10.4	10.6	11.8	8.6
SO_2 mg./liter	27	30	16	20	29	17	26	29	1	140	156	160
Volatile Acid exclusive of SO_2 (as acetic) g./100 ml.	0.049	0.028	0.036	0.057	0.052	0.044	0.043	0.082	0.063	0.103	0.176	0.296
Fixed Acid (as tartaric) g./100 ml.	1.12	1.07	0.86	0.77	0.89	0.75	0.72	0.62	0.55	0.48	0.42	0.29
Fusel Oil g./100 ml.	0.02	0.02	0.02	0.04	0.02	0.03	0.03	0.02	(too small to measure)			
Glycerol g./100 ml.	0.49	0.44	0.45	0.45	0.70	0.50	0.59	0.74	0.62	0.74	0.58	0.81
Esters (as ethyl acetate) mg./liter	61	64	38	41	72	80	75	78	78	75	110	131
Aldehydes (as acetaldehyde) mg./liter	32	45	26	15	23	25	13	12	11	17	54	40
Methanol g./100 ml.	0.004	0.004	0.006	0.005	0.007	0.007	0.008	0.009	0.004	0.008	0.010	0.012
Furfurans** (as furfural) mg./100 ml.	52	52	53	44	10	13	8	14	60	104	126	200

* Good fruit—Marketable for table consumption
Fair fruit—Slight decomposition, unmarketable
Poor fruit—General rotting
Very poor fruit—Extensive decomposition with loss of structure

** Substances which produce furfural when distilled with HCL

termined by the method of Lambert and Neish (24). Methanol was determined by the method of Boos (25). Esters and aldehydes were determined by the volumetric method for distilled liquors outlined in the A. O. A. C., 6th Edition, 1945, page 195. Furfurans (substances which produce furfural when distilled with hydrochloric acid) were determined as furfural by the method of Duncan (26).

Results of analyses are shown in Table I.

Taste

No fine distinction was attempted in the tasting of the wine samples. Wines were classed as acceptable or not. The wines from good fruit and from fair fruit were in each case acceptable; however, fruit which had undergone considerable rotting and decomposition produced wines with distinct moldy and musty tastes.

Color

In the loganberry wines there was a marked color difference in the wines made from good or poor fruit. Yang and Wiegand (27) have reported that the color of berry wines can be correlated directly with the quality of the wine and recommended that the ratio of the extinction coefficients at 515 and 340 millimicrons be used to indicate the degree of color destruction and the quality of the wine. Our results showed that the destruction of color also paralleled the spoilage of the loganberries used to make wine, as shown in Table II. All measurements were made with a Beckman Quartz Spectrophometer, Model DU on a solution of 10 per cent wine in water.

TABLE II. E_{515}/E_{340} Ratio in Loganberry Wines

	Condition of Fruit *			
	Good	Fair	Poor	Very Poor
Freshly made wine	1.028	0.598	0.261	0.109
1 month old	0.839	0.525	0.255	0.111
2 months old	0.779	0.480	0.238	0.106
3 months old	0.779	0.476	0.232	0.106
4 months old	0.658	0.456	0.226	0.101

* See Table I for description

Discussion

Probably the most general effect of spoiled fruit on the finished wine is the loss of the fixed acid even when there is sufficient sugar present to support the growth of microorganisms. Although no attempt was made to identify the molds or other organisms present, there is apparently no selectivity in acid destruction since each wine exhibited a decrease in fixed acid, which is somewhat less in grapes than in loganberries and apples. This decrease may be due either to microorganisms or to physiological changes in the fruit during storage.

Even though fruit has undergone spoilage, it is apparently unnecessary under laboratory conditions to use large amounts of sulfur dioxide in wine growing in order to produce a wine low in volatile acidity. In the case of apples even the use of comparatively large quantities of sulfur dioxide cannot prevent acetification which probably takes place before the juice is expressed.

The relatively high ester values found in wine made from fully spoiled apples are probably due to the presence of large amounts of volatile acid. The increasing values for methanol and furfurans in wines made from apples of increasing degrees of spoilage are no doubt due to the breakdown of the pectic substances present to give methanol, galacturonic acid and pentoses.

The color break in loganberries as they deteriorate is carried over to the wine made from them. It is evident from the results of the storage of these wines that the color destruction is greater and more rapid in wines of high natural pigment content.

Summary

A study of the effect of the use of spoiled fruit in making table type loganberry, grape and apple wines was made. Wines were analyzed by accepted methods for certain common constituents. In all wines, the fixed acid content decreased with increasing degrees of fruit spoilage. Methanol and furfural producing substances increased in apple wines with increasing degrees of fruit spoilage. Other factors such as fusel oil, glycerol, esters and aldehydes were not markedly changed whether wines were made from good or decomposed fruit.

Acknowledgment

The authors wish to thank Joe G. Hendrickson for his help with the analytical work.

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FIRST BIENNIAL REPORT OF THE LaWALL MEMORIAL LABORATORY OF PHARMACOLOGY AND BIOCHEMISTRY, PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE, 1950-1952

THE LaWall Memorial Laboratory of Pharmacology and Biochemistry, established at the Philadelphia College of Pharmacy and Science with the assistance of the estates of Dr. Charles Herbert LaWall, beloved Instructor, Professor, Dean at the College; his equally energetic wife, Millicent Renshaw LaWall; her loyal sister, Gabrielle H. Renshaw; and other generous friends, was dedicated May 17, 1950, together with the augmented Remington Memorial Laboratory of Pharmaceutical Manufacturing, and the Research Laboratory of the Bacteriology Department.

Under the chairmanship of Dr. Ivor Griffith, president of the College, the following addresses were delivered at the dedicatory exercises:

The Spirit of the Laboratory, John C. Krantz, Jr., Ph.D., D.Sc., Professor of Pharmacology, School of Medicine, University of Maryland.

The Spirit of Research, Stanley P. Reimann, M.D., Scientific Director, Institute for Cancer Research.

Pharmacy and Pharmacology in a Changing World, Carl F. Schmidt, M.D., Professor of Pharmacology, School of Medicine, University of Pennsylvania.

The Spirit of Integrated Health Sciences, S. P. Wetherill, Jr., B.Sc., LL.D., Chairman, Board of Trustees, Philadelphia College of Pharmacy and Science.

This event marked the fulfillment of careful planning by President Griffith for better facilities for continuing the early work of 1934-1942, during which time the original pharmacology laboratory was housed in the old farmhouse on Woodland Avenue, adjacent to the Kilmer Botanical Garden. The desirability of providing facilities for graduate teaching and research in Pharmacology and Biochemistry had long been evident.

Such courses would create new possibilities for graduates trained in these fields and help to supply academic, government and industrial research institutions with well trained individuals, the demand for which has far exceeded our resources in recent years.

Pharmacology and Biochemistry have become more and more important to pharmacists in our changing world. In earlier days, when the pharmacist, himself, produced most of his drugs, pharmacognosy and chemistry were his most important tools. Today, much of this work is provided by specialists in pharmaceutical manufacturing houses. The pharmacist, on the other hand, must know more and more about the biological actions of drugs. He must find new ways to compound and dispense the many new drugs which appear almost daily on the market. For this, he must have a good knowledge of the absorption, excretion, action and fate of these drugs in the human body. Often, he has to act as counselor to the physician in such matters.

Furthermore, industry, which produces the new drugs, needs qualified men and women to carry on these great developments. With the advance of public health, an increasing number of products (pharmaceutical and non-pharmaceutical) must be animal and otherwise tested for toxic and allergic actions. There is a great and growing need for toxicologists and bioassayists.

Studies in pharmacology and biochemistry also broaden the horizon of bacteriologists and biologists who may work later on in

Dr. Harrisson (left) Instructs Students
in Laboratory Technique

the field of chemotherapy of bacterial, virus and fungous diseases. The new laboratory was designed to provide a well equipped institution to perform vital research and to introduce students to what may be called "the spirit of research."

Organization

The original staff comprised Dr. Joseph W. E. Harrisson, Dr. Julian L. Ambrus and Dr. Clara M. Ambrus. In January 1950, in a bare, unequipped laboratory, they commenced their organizational work. By April, several research projects were under way, and by the date of dedication, the laboratory was practically complete in its equipment. Much of the credit for this rapid progress was due Mr. William D. Merkins and his maintenance and construction department of the College, building and installing equipment designed primarily by the staff.

An animal colony was organized which presently is able to produce about half of the experimental animals needed by the laboratory. The inbreeding of different mice strains needed for cancer research was also initiated. The staff is greatly indebted to Dr. Theodor Hauschka (Cancer Institute of Philadelphia), Dr. Clara J. Lynch, (Rockefeller Institute, N. Y.), Dr. Margaret Reed Lewis (Wistar Institute, U. of Pa.), Dr. M. N. Runner (Jackson Memorial Laboratory, Bar Harbor, Maine), Dr. Fraser (McGill University, Montreal, Canada), and Dr. E. E. Jones (Department of Zoology, Wellesley College) for providing a breeding stock from their highly valuable strains. The strains presently inbred in the animal colony are: C_{57}, C_{58}, C_3H, C_3H-t, RIL (AK), Strong A and 129. The laboratory also breeds Swiss mice, Sherman rats, Peromyscus maniculatus and English smooth hair guinea pigs.

Files of reprints and purchasing sources were started.

A small collection of drugs, reagents and reference standards was initiated.

A small but useful collection of bacterial, fungus and virus strains was established.

A modest departmental library was also created.

Students are trained in the importance of a proper place for each piece of equipment by making an inventory of the entire laboratory each semester.

Instruction

In January 1950, a seminar was organized to teach general principles and methods of research in pharmacology and biochemistry to senior students. These students were encouraged to prepare reviews or progress reports on certain subjects in these fields. Attendance at the seminar was voluntary, and no scholastic credits were given.

During the 1950 summer period, some of these same students were given the opportunity to work in the laboratory on a volunteer basis, without scholastic credit or compensation. They were assigned individually, or in teams, to different research projects planned by the staff. Our experience indicates that such "on the job" training is highly suitable to introduce students to the spirit of research work, and to build up enthusiasm for research and intensive study.

Seven students participated in this program, most of whom had previously attended the seminar. The participating students were Charles A. Leonard, B.S. in Pharmacy, 1950; Charles E. Moser, B.S. in Pharmacy, 1950; Howard Cravetz, B.S. in Bacteriology, 1950; George V. Rossi, senior in Pharmacy; Elias W. Packman, senior in Pharmacy, Arthur Green, M.S. in Bacteriology, 1950; Sirka Maczuk, junior in Pharmacy.

The first mentioned five students continued their research projects even after college started in September. They worked mainly in the evenings and on Saturdays. In spite of these strenuous and time-consuming activities, most of them achieved the top rank of their respective classes. In January, 1951, another volunteer worker, Erwin Diner, B.S. in Pharmacy, 1939, joined the group.

The first regular courses for graduate students were inaugurated in the Fall of 1950. Originally, eight students attended these courses, four majoring in Pharmacology, and four taking this subject as a minor. The major fields of those minoring in Pharmacology were as follows: bacteriology, three; pharmacy, one. The courses offered that year were: physiology, pharmacodynamics and biological assay. They were taken jointly and consisted of five lecture hours and twelve laboratory hours each week for two semesters. In addition to the class work, the students were required to check daily on their experimental animals and instruments if necessary. Instruction was also given in methods of chemotherapeutic research and the Warburg technique.

Three of the graduate students prepared their theses in this laboratory. Two were pharmacology majors, and one a major in bac-

teriology who worked under the joint guidance of the staffs of the departments of bacteriology and pharmacology.

Five students were candidates for the Master's degree in 1951.

Four of the students were candidates for predoctoral fellowships for the year 1951-52. One student received an Atomic Energy Commission Fellowship to work on a research project proposed by the staff.

Members of the staff during the year also taught undergraduate pharmacology and bioassay classes. During these lectures frequent demonstrations of experimental procedures were given.

The staff prepared in preliminary form a mimeographed laboratory manual in physiology, pharmacology and bioassay for graduate students and a pharmacology text for undergraduates.

In the second year of teaching (1951-52) under the direction of the LaWall Laboratory Staff, the following courses were conducted:

Pharmacodynamics, for junior students, two hours per week (J. Ambrus, C. Ambrus, Harrisson).

Bioassay, for senior students, one hour per week (Harrisson).

Pharmacology recitation, for senior students, two hours per week (Packman).

Physiology, Pharmacology, Bioassay, for graduate students (with laboratory work), 16 hours per week (J. Ambrus, C. Ambrus, Harrisson).

Advanced Pharmacology, for graduate students (with laboratory work), nine hours per week (Harrisson, J. Ambrus, C. Ambrus).

Pathologic Aspects of Physiology and Biochemistry, for graduate students, one hour per week (C. Ambrus, J. Ambrus).

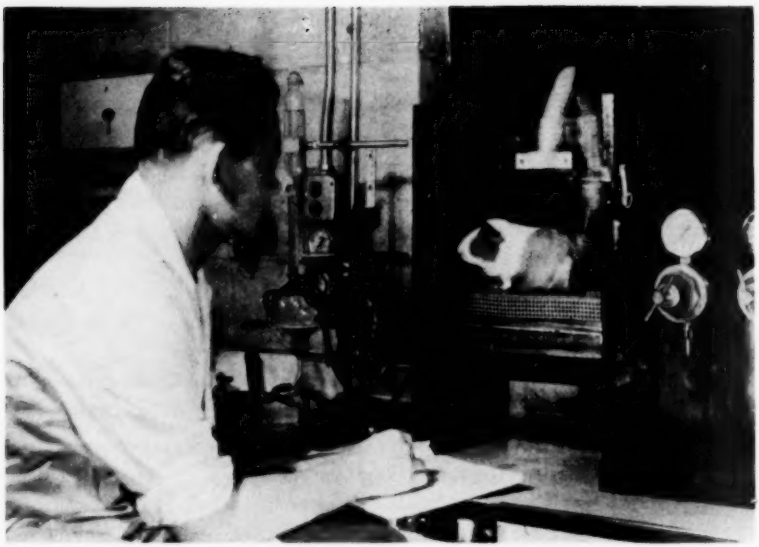
Immunology, for graduate students, one hour per week for one semester (C. Ambrus, J. Ambrus).*

Hematology, for graduate students, one hour per week for one semester (C. Ambrus, J. Ambrus.)*

Toxicology, for graduate students, one hour per week for one semester (Harrisson, J. Ambrus.)*

Pharmacology Research, for graduate students, minimum of ten hours per week (Harrisson, J. Ambrus, C. Ambrus).

Pharmacology Seminar, for graduate students, one hour per week (Harrisson, J. Ambrus, C. Ambrus).



Testing of Antihistamines
By Aerosol Technique

The courses marked * are to be given in alternate years only, and the following will be given in the intervening years:

Pathologic Aspects of Anatomy and Histology, for graduate students, one hour per week (C. Ambrus).

Nutrition, for graduate students, one hour per week (Harrisson, J. Ambrus).

(It is to be noted that five additional courses for undergraduates are conducted by the Pharmacology Department, but members of the LaWall Laboratory Staff are not involved.)

Program Now Offered for Master's Degree

A definite course of study is now offered to holders of the B.Sc. in Pharmacy degree, through work leading to the M.Sc. in Pharmacy, with concentration on Pharmacology and related subjects.

The following studies are required for completion of the course:

Course	*Clock Hours* *Lecture*	*Laboratory*	*Credits*
Physiology	2	3	6
Pharmacology	2	6	8
Bio-Assay	1	3	4
Therapeutic Aspects of Pharmacology	1	—	2
Advanced Pharmacy	1	2	4
Pharmacy Seminar	1	—	2
Physical Chemistry	1	3 (2nd Sem.)	3½
Biochemistry	2	—	4

There is also offered to holders of the B.Sc. in Biology or any other degree of equivalent training (which must include a fundamental course in Pharmacology) a course of study leading to the M.Sc. in Biology, with concentration on Pharmacology and related subjects.

The following studies are required for completion of the course:

Course	*Clock Hours* *Lecture*	*Laboratory*	*Credits*
Physiology	2	3	6
Pharmacology	2	6	8
Bio-Assay	1	3	4
Therapeutic Aspects of Pharmacology	1	—	2
Biology Seminar	1	—	2

The student in this course is expected to take additional elective subjects to the extent of approximately 10 credits. These will be chosen by the student, subject to the approval of the Graduate Committee.

It is understood that the undergraduate degrees mentioned as prerequisite to entrance into these programs are those granted by this institution or are equivalent thereto.

Program for the Doctorate

Students who have completed either of the foregoing programs, or their equivalent, will have an opportunity to continue their educa-

tion in the field of Pharmacology and to engage in research in that field. Such work may lead to the degree of Doctor of Science, either in Pharmacy or in Biology. The program of each student will be arranged by the Heads of the Department of Pharmacology and of the Department in which the degree is to be granted, and will be subject to the approval of the Graduate Committee.

The following courses are required:

Advanced Pharmacology (Lecture and Laboratory)
Introduction to Calculus and Statistics
History of Science
Pathologic Aspects of
(a) Physiology
(b) Biochemistry
(c) Histology
(d) Anatomy

Hematology
Immunology
Nutrition
Toxicology
Pharmacology Seminar

In addition, the student is expected to have earned credits in the following courses, or to take them simultaneously with his graduate program:

Mammalian Anatomy
Histology
Embryology
Colloid Chemistry
Analysis of Medicinals (Lecture)
Chemistry of Synthetic Medicinals (Lecture)

The student must also satisfy the general requirements for the Doctor of Science degree, as set forth in the College Catalogue.

Audio-Visual Aids

The laboratory has now a considerable collection of lantern slides on pharmacological subjects, and of pathological specimens, mainly of neoplastic diseases of experimental animals.

For the past two years motion pictures have been shown once each week on Wednesday following the normal school day. All students were invited to attend these showings, and attendance, though voluntary, was highly gratifying to the staff who chose and exhibited the films.

In this time, the following pictures were projected:

Abbott Laboratories
- The Lymphatic System

American Medical Association
- Dynamics of Respiration
- Signs of Inhalation Anesthesia
- Syphilis

Armour Laboratories
- Bone Marrow
- Physiology and Pathology of Hemopoietic Principles
- Tryptar

Becton, Dickinson and Company
- Techniques of Infection
- Hospital Care of Syringes and Needles

Bilhuber-Knoll Corporation
- Pharmacolgic Study of Metrazol
- Mechanism of the Heartbeat

Bray Pharmaceutical Corporation
- Digestive Tract

British Information Service
- Papworth Village Settlement
- Malaria

Ciba Pharmaceutical Products Inc.
- Pharmacology of Respiratory Stimulants (Coramine)

Columbia University
- Conditioned Reflexes and Behavior

Eli Lilly and Company
- Nicotinic Acid Deficiency
- Riboflavin Deficiency
- Thiamin Chloride Deficiency
- Kidney Function in Disease
- Kidney Function in Health

Encyclopedia Britannica
- Control of Body Temperature
- The Nervous System
- Mechanism of Breathing
- The Alimentary Tract
- Heredity
- Digestion of Foods
- Tuberculosis

Imperial Chemical Industries
- Signs and Stages of Anesthesia
- The Function of the Carotid Sinus and Aortic Nerve

Lederle Laboratories
- Vitamins and Some Deficiency Diseases
- The Anemias
- Sulfonamide Therapy

Mallinckrodt Chemical Works
- Advent of Anesthesia
- Ether for Anesthesia

Mead Johnson and Company
- Ascorbic Acid and Scurvy

Medical College of South Carolina
- Cardiac Arrythmia
- Cannula Sequence
- Contractile Force of Heart Using Strain Gauge
- Technic of Digestion in Animals
- Effect of Drugs on Gut Movement

Moody Bible Institute
- Dust or Destiny

Ralston-Purina Company
- Where Chick Life Begins

Sandoz Chemical Works, Inc.
- Epilepsy

Schering Corporation
- Physiology of Normal Menstruation
- The Male Sex Hormone

Society of American Bacteriologists
- Life Cycle of Trichinella Spiralis

United States Army Medical Library
Respiratory Reflexes in the Rabbit
Carotid Bodies and Respiration
Ascariasis
The Radioisotopes
Heart-Lung Preparations (b)

United States Public Health Service
Chick Embryo Techniques

The Upjohn Company
Energy Release From Food

Wistar Institute
Mesenteric Lymphatics
Effect of Drugs on Lymphatics

Wyeth Incorporated
Movements of Alimentary Tract in Experimental Animals
Allergy-Immunology and Treatment
Clinical Use of Hyaluronidase

Research

Basic investigations have been carried out in the LaWall Laboratory, resulting in papers contributed to the scientific literature, and listed in the concluding portion of this report.

A number of graduate theses have been written on the basis of work in this laboratory, and the following recipients of graduate degrees from the College concluded major studies in pharmacology on the subjects which became their thesis titles:

1951

Master of Science in Bacteriology

Howard Cravetz
"Natural Antibodies in Rabbits, Guinea Pigs and Hamsters"

Master of Science in Pharmacy

Charles A. Leonard
"Chemotherapeutic Studies in Hyperthermic Shock"

Charles E. Moser
"The Effect of Antihistamine Drugs on Experimental Vomiting"

1952

DOCTOR OF SCIENCE IN BACTERIOLOGY

Arthur E. Greene

"The Effect of Certain Shock Substances on Cl. tetani, Its Spores and Toxins"

MASTER OF SCIENCE IN PHARMACY

Nahum M. Balotin

"The Desensitization Toward Certain Shock Substances During the Development of Resistance Toward the Noble Collip Shock"

Charles K. Gorby

"Effect of Cortisone and Desoxycorticosterone on Barbiturate Poisoning"

Elias W. Packman and George V. Rossi (in collaboration)

"Studies on the Effect of Histamine and Antihistamines on Body Temperature"

David C. Schechter

"The Effect of Dicumarolization on the Thromboplastic Potency of Rabbit Brain"

All minor students were assigned term papers on subjects in pharmacology.

Research Grants and Fellowships

Eli Lilly and Company have established a research grant in this Department for the study of the therapy of barbiturate poisoning. In collaboration with Dr. Nathan Rubin, of the Organic Chemistry Department, some new chemical agents will be synthesized and tested by Mr. Charles A. Leonard.

Under a grant from the Lederle Laboratories, Miss Catherine N. Sideri is conducting a study on the effect of certain antibiotics on virus infections.

A fellowship from the Atomic Energy Commission enables Charles E. Moser to study certain aspects of irradiation sickness and shock.

LaWall and Harrisson Laboratories, on behalf of the American Chicle Company, have established a grant for the investigation of the metabolism and effects of chlorophyll.

The Present Staff

Director

Joseph W. E. Harrisson, Phar. D., D.Sc., Associate of the late Dr. Charles H. LaWall, Director of LaWall and Harrisson, Consultants; Chairman, Pennsylvania Department Agriculture, Board of Consulting Chemists; Secretary of the American Board of Clinical Chemistry, Inc.

Assistant Director

Julian L. Ambrus, B.Sc., M.D., Associate Professor of Pharmacology, formerly on the Research Staff, Pasteur Institute, Paris, formerly assistant, University of Zurich Medical School.

Associate

Clara M. Ambrus, B.Sc., M.D., Assistant Professor of Pharmacology, formerly of the Research Staff, Pasteur Institute, Paris, formerly assistant, University of Zurich Medical School.

The following graduate students have participated in research projects in the laboratory, in collaboration with the above-mentioned staff:

N. Malcolm Balotin
Harris Bernstein (also a member of the teaching staff in Pharmacy)
Louis Cipriany
Charles E. Gorby
Gilbert C. Johnson
Charles A. Leonard
Charles E. Moser
Elias Packman (also instructor in Pharmacology in undergraduate work)
George V. Rossi (also a member of the teaching staff in Pharmacy)
David C. Schechter
Catherine N. Sideri (also a member of the teaching staff in Chemistry)

Mrs. E. Mihalyi serves as laboratory technician, and Mr. Theodore R. Lewandowski has replaced Mr. B. Rivers, who was called to military service, as animal attendant.

Left—Operating Team Removing Rabbit Testicles in Studies With Myxomatosis Virus

Right—Drs. Clara and Julian Ambrus Reading Agglutination Tests

Staff Activities

In the two years of the work of the Laboratory, members of the staff have delivered numerous lectures to learned organizations, scientific societies, research groups and civic organizations. Demonstrations have been conducted at many meetings throughout the country, and both junior and senior members of the staff have participated in seminars and panel discussions at various scientific gatherings. Sev-

eral staff members served as collaborators, reviewers and abstract writers for scientific journals.

Many visitors, singly and in groups, have been conducted through the LaWall Laboratory on tours of inspection by members of the staff.

PUBLICATIONS FROM THE LABORATORY 1950-1952

(Several minor papers, laboratory notes, etc. are not included in this list)

Effect of antihistamines on viruses of the influenza group. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Am. J. Pharm. *123*, 60. (1951)

Mechanism of the liberation of histamine in anaphylactic shock. J. W. E. Harrisson, C. M. Ambrus, J. L. Ambrus. Am. J. Pharm. *123*, 282. (1951)

Synergistic effect between histamine, antihistamines and hypnotic drugs. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson, Ch. E. Moser, Ch. A. Leonard. Read before the AAAS meeting 1951 in Philadelphia. J. A. Ph. A. in press.

A simple aerosol chamber. J. W. E. Harrisson, J. L. Ambrus, C. M. Ambrus. J. A. Ph. A. *11*, 226. (1951)

Effect of histamine, antihistamines and histamine desensitization on the gastric secretion of rats and guinea pigs. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Read before the A. Ph. A. meeting, 1951 in Buffalo. Submitted for publication.

Effect of histamine desensitization on histamine induced gastric secretion of guinea pigs. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Gastroenterology *18*, 249. (1951)

Mode of action of histamine desensitization. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Am. J. Physiol. *167*, 268. (1951)

Effect of histamine and antihistamine on the liberation of certain "shock substances." J. L. Ambrus, C. M. Ambrus. Read before the Physiological Society, Phila. 1951. Am. J. Med. Sci. *223*, 216. (1952)

Tolerance of rats toward amphetamine and methamphetamine. J. W. E. Harrisson, C. M. Ambrus, J. L. Ambrus. Read before the AAAS meeting in Philadelphia in 1951. J. A. Ph. A. in press.

Comparison of methods for obtaining blood from mice. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson, Ch. A. Leonard, Ch. E. Moser, H. Cravetz. Am. J. Pharm. *123*. 100. (1951)

Effect of Thorotrast on anaphylactic phenomena. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Acta Allergologica *4*. 201. (1951)

Chronic and topical toxicity of zirconium carbonate. J. W. E. Harrisson, Bernard Trebin and Eric Martin. Jour. Pharm. and Exp. Therap. 102, 179. (1951)

Effect of reticuloendothelial blockade by Thorotrast on the development of normal heterohemagglutinins in fowl. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Experientia *7*, 382. (1951)

Study on the hetero-transplantation of Ehrlich carcinoma in relation to antibody formation. J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Am. J. Pharm. *123*, 19. (1951)

Effect of adenosine triphosphate, adenosine-5-phosphoric acid and adenosine-3-phosphoric acid on Ehrlich carcinoma. C. M. Ambrus, J. L. Ambrus, J. W. E. Harrisson, H. Cravetz. Brit. J. Cancer. *5*, 311. (1951)

Antagonism and synergism between histamine and antihistamines. J. L. Ambrus, E. W. Packman, G. V. Rossi, J. W. E. Harrisson. J. Pharm. Pharmacol. (Brit.) *4*, 466. (1952)

Immunological relationship between fibroma and myxoma viruses. C. N. Sideri, J. L. Ambrus, C. M. Ambrus, J. W. E. Harrisson. Am. J. Vet. Med. in press.

Effect of drugs on oxygen consumption of virus infected tissue cultures. J. L. Ambrus, C. M. Ambrus, C. N. Sideri, J. W. E. Harrisson. Fed. Proc. 11. No. 1 (1952)

Acute poisoning with 1080 with note on the distribution of fluoroacetate in the organism. J. W. E. Harrisson, J. L. Ambrus, C. M. Ambrus, L. C. Reese, R. H. Peters, T. Baker, E. W. Rees. J. A. M. A. in press. (Nov. 1952)

Fluoroacetate poisoning. J. W. E. Harrisson, J. L. Ambrus, C. M. Ambrus. A review. In press. J. Indus. Med. & Surg. (Sept. 1952)

Effect of histamine on the convulsive effect of antihistamines. D. C. Schechter, J. W. E. Harrisson, J. L. Ambrus, C. M. Ambrus. J. A. Ph. A. In press.

Toxicity of penicillin and aureomycin in guinea pigs. C. M. Ambrus, C. N. Sideri, G. C. Johnson, J. W. E. Harrisson. In press. Antibiotics and Chemotherapy.

Effect of the mammary tumor agent on species other than the mouse. C. M. Ambrus, J. L. Ambrus, J. W. E. Harrisson. Submitted for publication.

Effect of broad spectrum antibiotics on tumor inducing viruses. J. L. Ambrus, C. M. Ambrus, C. N. Sideri, J. W. E. Harrisson. Submitted for publication.

SELECTED ABSTRACTS

Succinylcholine Iodide as a Muscle Relaxant. Anon. *The Alchemist 10*:182 (1952). In Sweden and in Great Britain succinylcholine iodide or chloride has been finding increasing use as a muscle relaxant. These salts act similar to decamethonium but differ from *d*-tubocurarine in their mode of action. They apparently depolarize the end-plate region of the skeletal muscles, probably by inhibiting the acetyl-cholinesterase of the red cells at the neuromuscular junction. The duration of action, with an intravenous dose of about 1 mg. per Kg. of body weight, was found to be from 2 to 10 minutes in most patients but as long as 20 minutes in a few patients. The possibility was suggested that the duration of action is dependent upon the removal of the drug by the "pseudo" cholinesterase of the blood serum. In those patients where the duration of action was long the serum esterase level was found to be quite low. It was thus suggested that in such cases succinylcholine salt should probably not be given.

The period of muscular relaxation is preceded by a period of muscular twitching which takes place about 15 seconds after injection and lasts about 15 to 20 seconds. After the contractions cease the muscle relaxation begins. Following the period of relaxation muscular power begins to return and is back to normal in 3 or 4 minutes. The period of muscular relaxation can be lengthened or shortened somewhat by increasing or decreasing the dose from the usual dose of about 1 mg. per Kg. Apparently a dose of more than 150 mg. does not prolong the period of relaxation because of the rapidity with which the succinylcholine is removed.

Side effects were almost non-existent in normal single doses. Administration of the drug by intravenous drip did cause a rise in blood pressure. Effective doses always caused respiratory arrest and this had to be counteracted by inflating the lungs with oxygen or with artificial respiration. A total of 1196 patients were reported as having received the drug. It was felt to be most useful in short procedures such as intubation, orthopedic manipulations, modifying electro-convulsive therapy, and similar procedures.

The Preparation of Stable Solutions of Crystalline Penicillin. Swallow, W. *Pharm. J. 168*:467 (1952). The preparation of stable solutions of crystalline penicillin has not been too successful. Various buffer systems have been employed but none has been as satisfactory as was desired. The author found that the gradual deepening of the yellow color of penicillin solutions and the subsequent appearance of a precipitate appeared to be retarded by the presence of sodium ethylene-diamine-tetra-acetate (Irgalon). The author, therefore, studied the effect of this compound on unbuffered solutions of sodium penicillin as well as on citrate buffered solutions, all containing 250,000 units of sodium penicillin per cc.

The results indicate that Irgalon increases the stability of the solutions. Concentrations of 1:500 or 1:250 seemed to be the best when used with β-phenoxy-ethyl-dimethyl-dodecyl-ammonium bromide (Bradosol) as the bactericide. A citrate buffered solution of penicillin containing Irgalon 1:250 showed 98 per cent of its potency retained after 35 days storage at 4° C. but a similar solution of penicillin, containing only phenol, showed only 9.4 per cent of its potency remaining after 35 days storage at the same temperature. At room temperature the Irgalon-protected, buffered solution showed a potency of 78.2 per cent after 14 days while the phenol-protected, buffered solution showed a potency of 52.7 per cent after the same period. Irgalon seemed to have very little protective effect at the boiling temperature.

Irgalon, a sequestering agent, has also been shown to prevent the oxidation of ascorbic acid solutions and to prevent the crystallization of supersaturated solutions of calcium gluconate. The author suggested that its action in stabilizing solutions of penicillin may be due to an inactivation of traces of heavy metals.

The toxicity of Irgalon is quite low. In rats the LD50 is given as 5 Gm. per Kg. and for mice as 2.4 Gm. per Kg. by mouth. Assuming as many as 8 injections in 24 hours the total amount of Irgalon would be 16 mg., or about 0.25 mg. per Kg. for the average man.

A Scheme for Antibiotic Action of Combinations. Jawetz, E. and Gunnison, J. B. *Antibiotics and Chemotherapy 2*:243 (1952). As a result of *in vivo* and *in vitro* studies the authors developed two groupings for the clinically useful antibiotics with regard to antag-

onism and synergism. Group I was composed of penicillin, streptomycin, bacitracin, and neomycin. Group II was composed of aureomycin, chloramphenicol, terramycin, and probably sulfonamides.

Synergism was defined as the ability of two drugs to increase markedly the rate of early bactericidal action or the rate of cure of experimental or clinical infections beyond that obtainable by simple additive effect. Antagonism was defined as a marked decrease in these properties below those observed with a single drug.

The authors reported that they found that the members of group I were frequently synergistic with each other, occasionally indifferent, but never antagonistic. They also found that for one antibiotic to be a member of a synergistic pair it must have some antibacterial action against the microorganism, even though the dose required may be far above that required in the combination showing synergism. The members of group II were found to be neither synergistic with, nor antagonistic to each other, but they were occasionally additive.

Susceptibility of the particular bacterial strain was found to be the determining factor in the effects obtained with combinations of members of group I and of group II. If the microorganism is found to be sensitive to a group I antibiotic, then a group II drug will frequently be found to be antagonistic. In the reverse circumstance, however, drugs of group I are not antagonistic to the action of group II drugs. In another situation, if a particular bacterium is resistant to group I antibiotics, but can be inhibited by a large dose, then a combination of a group I antibiotic and a group II drug will sometimes produce synergism but never antagonism.

BOOK REVIEWS

Biological Antagonism. By Gustav J. Martin, The National Drug Co. vii + 516 pages. The Blakiston Company, Philadelphia, Pa. Price $8.50.

The concept of biological antagonism, which explains numerous physiological reactions and pathological conditions on the basis of structural displacement in biological systems, is new. The period 1920 to 1940 witnessed the evolution of theories concerning haptens, inhibiting analogues of amino acids and hormones, cholinesterase inhibitors, antivitamins, antienzymes, and numerous other antimetabolites.

Dr. Martin's volume is the first comprehensive attempt to interpret these data in a logical manner. The ideas he presents are stimulating and indicate his appreciation of the broad scope of biochemistry. His coverage of the field is thorough, and the text is well documented and amply illustrated with tables and formulas. There are a few inconsistencies and inaccuracies in the structural formulas, but in general the book has been carefully proof-read.

Every investigator, teacher and student of biochemistry and the related biological sciences will find that this volume will be a valuable addition to his library.

ERIC W. MARTIN

Skin Therapeutics. M. K. Polano, M. D., The Hague (Netherlands). Elsevier Publishing Company, Houston, Texas. xvi + 276 pp. Price $6.50.

This book differs from others in the dermatology field in that the author makes no effort to outline the treatment of specific diseases, but rather devotes himself entirely to a detailed discussion of the general principles of topical therapy. The author states that his aim is "to stress the importance of the art of prescribing, which is seriously threatened by the modern trend of prescribing proprietary ready-made ointments".

The book, which contains an introduction by the noted American dermatologist, Dr. Clarence S. Livengood, covers the following topics:

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2. The Basic Materials
3. The Use of the Basic Material in Prescriptions
4. Specific Drugs
5. Selecting the Ointment Base in Various Dermatological Conditions
6. The Effect of Drugs on the Skin in Relation to the Base

This is by far the most enlightening work on the principles of topical dermatological therapy that the reviewer has had the pleasure of reading. The author, an active European researcher in the field of dermatology, fully recognizes that a really sound scientifically based foundation for the evaluation of dermatological preparations is yet to be realized. He is fully cognizant that the physician and pharmacist must fully cooperate in the formulation of dermatologicals for optimum results.

By continually referring to the recognized preparations of the official formularies of the United States, Great Britain, Switzerland and Holland, the author attempts to cement international understanding among those interested in dermatology in various lands; the nomenclature problems being greatly simplified.

This book is highly recommended for use by the students and practitioners in the fields of dermatology and pharmacy. It is indeed an unique work.

M. Barr

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